A1 cont.

following angioplasty based interventions and reduction/stabilization of plaques in atherosclerotic lesions.

B. Replace the paragraph at page 6, line 12 through page 6, line 21 with the following paragraph:

A2

A third factor that has led researchers to rely on wavelengths greater than 630 nm is based on the geometric falloff of light emitted from a cylindrical or point source. As light radiates outward from either a cylindrical source or a point source, it must decrease in intensity since it is gradually spread over an ever-increasing volume. This conclusion is a result of basic physics and is simply a consequence of the law of conservation of energy. Furthermore, even in the red/infrared portion of the spectrum, light undergoes relatively strong absorption and scattering by tissue. Therefore, in addition to the geometric falloff, both absorption and scattering limit the penetration depth of light into surrounding tissues, even in the red/infrared portion of the spectrum. The combination of this, along with the previously mentioned factors, has led to the exclusive use of wavelengths of 630 nm and greater in cardiovascular PDT studies to date.

C. Replace the paragraph at page 7, line 18 through page 8, line 14 with the following paragraph:

A3

We have discovered that photosensitizer selectivity alone is insufficient to ensure minimal damage to surrounding tissue while simultaneously providing the desired level of efficacy within the targeted cardiovascular tissue. A wide variety of tissue types, such as myocardium, lung, nerves, adjacent vessels, fat, etc. are typically located near target vessels. In practice, it is nearly impossible for a drug to have the necessary preferential uptake characteristics in the target tissue, while not being taken up to some degree in these surrounding tissues as well. We have found that in situations where such surrounding tissues contain some amount of the photosensitizer, there is an especially difficult challenge in the practical implementation of PDT using red/infrared light. Penetration of light in this wavelength range appears to cause undesired PDT treatment in important underlying tissues that are well beyond the desired treatment zone of the vessel, thereby making it difficult to control treatment depth. Furthermore, while in theory it might be possible to accurately control the treatment depth by delivery of a specific light dose at

the surface of the vessel lumen, this may be difficult to achieve in practice, due to the variations in tissue optical properties as well as the difficulty in accurately controlling the light level at all surfaces when using intravascular light. Furthermore, drug uptake will vary within the target treatment zone (even for the same tissue type) and the optical properties of the target tissue will vary between patients. These various factors will lead to significant practical limitations associated with variations in treatment depth, especially for wavelengths of 630 nm and greater. In practice, some regions in the target treatment area will receive an insufficient depth of treatment while others well outside the target treatment area will incur detrimental PDT effects.

A3 cont.

D. Replace the paragraph at page 8, line 15 through page 8, line 17 with the following paragraph:

Accordingly, there is a continuing need for a cardiovascular PDT treatment that delivers light to sufficiently penetrate into the target tissue, while simultaneously preventing the light from significantly penetrating through the tissue surrounding the target area.

A4

E. Replace the paragraph at page 8, line 19 through page 10, line 6 with the following paragraph:

A5

The present invention involves excitation of photosensitizer drugs for treatment of cardiovascular occlusions using wavelengths selected to improve efficacy and safety over previous approaches. Through the use of wavelengths in the 390-610 nm range, there is minimal surrounding tissue damage and simultaneously a very significant PDT effect is achieved within the vessel which is the target of the treatment. Selection of the particular range of wavelengths is based on the scattering properties of tissue and the detailed absorption spectrum of hemoglobin and the critical role they play in light penetration in tissue. Absorption and scattering preferably prevents light from penetrating as deeply as with wavelengths in the red/infrared portion of the spectrum. In particular, at wavelengths in the 390-610 nm region, the optical penetration depth is comparable to the desired depth of treatment in cardiovascular applications of PDT. This in turn provides a means to eliminate many of the disadvantages that have been identified above for red or infrared light. Within the spectral region of 390-610 nm, the region of 440-610 nm is preferred when using devices that provide less efficient blood elimination or when a deeper depth of treatment is desired. This more restricted range

is based on the fact that these wavelengths are on the long wavelength side of the Soret band for hemoglobin, thus there is not the severe attenuation by blood that exists for the shorter wavelengths. This method thereby allows sufficient penetration to treat thicker vessels to the desired depth in a reasonable time. This technique is applicable to all photosensitizers with sufficient absorption in this wavelength region. Here, sufficient absorption means an absorption coefficient high enough to allow treatment within a clinically relevant time period using available laser sources and allowable drug doses. This invention applies to, but is not limited to, photosensitizers of the following classes: texaphyrins, benzoporphyrin derivatives (including Visudyne), azaporphyrins, phthalocyanines, purpurins, Rose Bengal, xanthenes, porphycyanines, isomeric porphyrins, pentaphyrins, sapphyrins, phlorins, benzochlorins, hypericins, anthraquinones, rhodanols, barbituric acid derivatives, expanded porphyrins, dipyrromethenes, coumarins, azo dyes, acridines, rhodanine, azine derivatives, tetrazolium derivatives, safranines, indocyanines, indigo derivatives, indigo triazine derivatives, pyrrole derived macrocyclic compounds, naturally occurring or synthetic porphyrins, naturally occurring or synthetic chlorines, naturally occurring or synthetic bacteriochlorins, naturally occurring or synthetic isobacteriochlorins, naphthalocyanines, phenoxazine derivatives, phenothiazine derivatives, chaloorganapyrylium derivatives, triarylmethane derivatives, rhodamine derivatives, fluorescein derivatives, verdin derivatives, toluidine blue derivatives, methylene blue derivatives, methylene violet derivatives, nile blue derivatives, nile red derivatives, phenazine derivatives, pinacyanol derivatives, plasmocorinth derivatives and indigo derivatives (included in this list is any combination of these photosensitizers as well as these photosensitizers in combination with other chemical substances).

A5 Cont.

F. Replace the paragraph at page 11, lines 5-6 with the following paragraph:

Figure 5 is an image of a porcine heart harvested at 3 days after receiving PDT in a coronary artery using MV6401 and intravascular red light (approximately 664 nm);

A6

G. Replace the paragraph at page 11, lines 7-8 with the following paragraph:

A7

Figure 6 is an image of a porcine heart harvested at 3 days after receiving PDT in a coronary artery using MV6401 and intravascular blue light (approximately 458 nm);

H. Replace the paragraph at page 11, lines 9-10 with the following paragraph:

A8

Figure 7 is an image of a porcine heart harvested at 3 days after receiving PDT in a coronary artery using MV6401 and intravascular green light (approximately 532 nm);

I. Replace the paragraph at page 12, line 12 through page 13, line 23 with the following paragraph:

A9

The present invention provides a method for PDT treatment to inhibit, stabilize or reduce occlusions in the cardiovascular system by exciting photosensitizer drugs using intravascular light at a wavelength in the range of 390-610 nm. While investigators in the PDT field have consistently pointed out the advantages of using red/infrared light excitation, our results, while inconsistent with those viewpoints and unexpected, indicate that alternative wavelengths which are less penetrating will provide an improved method of treatment. The previous approach of using red/infrared wavelengths was based in part on taking advantage of the fact that the attenuation of light by tissue and blood reaches a minimum in the red/infrared part of the spectrum. However, we have discovered that, in direct contrast to this view, wavelengths outside this red/infrared spectral region are optimal for PDT-based cardiovascular treatments. While in theory, wavelengths in the mid-infrared could be used, we have found that the most effective wavelengths are those coincident with spectral regions of significant absorption by hemoglobin, in particular, wavelengths in the 390-610 nm range. This choice of wavelength range is based on the objective of providing a practical, safe and effective PDT treatment. Wavelengths less than 390 nm are in the ultraviolet portion of the spectrum. Such wavelengths have several drawbacks including absorption by other chromophores within tissue, potential for mutagenicity, lack of convenient light sources and tendency to cause light-induced damage of optical components. In the case of 610 nm, this wavelength corresponds to the onset of strong absorption by hemoglobin in blood, as hemoglobin has a relatively strong absorption for light having wavelengths less than approximately 610 nm. Therefore, by using excitation sources having wavelengths of 610 nm or shorter, one

may take advantage of hemoglobin absorption to limit the PDT treatment to the target treatment zone. This approach appears to limit the degree of surrounding tissue damage to an acceptable level and simultaneously provides a significant PDT treatment in the target tissue, which was not practical with the approach of the prior art. Furthermore, to be effective, the preferred method uses this concept with photosensitizers having relatively strong absorption (greater than 1000 L cm^{-1} M^{-1}). Photosensitizers having absorption coefficients less than this cannot be efficiently excited, resulting in the need to use high light irradiances, high light doses or high drug doses. High light irradiances can lead to thermal injury while high light doses require long treatment times and high drug doses raise the prospect of drug related toxicities. An advantage of PDT photosensitizers over other photoactive molecules, such as psoralens, is their absorption spectra. Specifically, PDT photosensitizers typically have relatively strong absorption features within this ideal spectral range that allow them to be efficiently excited using wavelengths within the range of 390-610 nm. Furthermore, PDT photosensitizers are not believed to significantly penetrate the cell nucleus, thereby avoiding any questions of treatment related mutagenic effects as have been raised with alternative therapies, such as psoralen based therapies.

A9 cont.

J. Replace the paragraph at page 15, line17 through page 16, line 2 with the following paragraph:

This invention may require removal of blood from the region between the light delivery device and the target tissue. For devices in which a limited amount of blood remains in this region or for which moderately deep treatment is desired, excitation in approximately the 440-610 nm range is preferred due to the relatively higher absorption by blood than occurs at shorter wavelengths. Specifically, wavelengths of approximately 440 nm and greater are on the long wavelength side of the Soret band for hemoglobin, such that for these wavelengths there is not the severe attenuation by blood that exists at shorter wavelengths. On the other hand, for devices that provide very efficient removal of blood, all wavelengths in the 390-610 nm range are effective.

A10

K. Replace the paragraph at page 16, lines 3-20 with the following paragraph:

This technique is applicable to all photosensitizers with sufficient absorption in this wavelength region. Here, sufficient absorption

A11

means an absorption coefficient high enough to allow treatment within a clinically relevant time period using available laser sources and allowable drug doses. The preferred value of the molar extinction coefficient at the treatment wavelength is about 1000 L cm^{-1} M^{-1} or greater. Compounds meeting these criteria include, but are not limited to, the following list of chemical classes, their derivatives and combinations of these: texaphyrins, benzoporphyrin derivatives (including Visudyne), azaporphyrins, phthalocyanines, purpurins, Rose Bengal, xanthenes, porphycyanines, isomeric porphyrins, pentaphyrins, sapphyrins, phlorins, benzochlorins, hypericins, anthraquinones, rhodanols, barbituric acid derivatives, expanded porphyrins, dipyrromethenes, coumarins, azo dyes, acridines, rhodanines, azine derivatives, tetrazolium derivatives, safranines, indocyanines, indigo dyes, triazine derivatives, pyrrole derived macrocyclic compounds, naturally occurring or synthetic porphyrins, naturally occurring or synthetic chlorines, naturally occurring or synthetic bacteriochlorins, naturally occurring or synthetic isobacteriochlorins, naphthalocyanines, phenoxazine derivatives, phenothiazine derivatives, chaloorganapyrylium derivatives, triarylmethane derivatives, rhodamine derivatives, fluorescein derivatives, verdin derivatives, toluidine blue derivatives, methylene blue derivatives, methylene violet derivatives, nile blue derivatives, nile red derivatives, phenazine derivatives, pinacyanol derivatives, plasmocorinth derivatives and indigo derivatives.

A11 cont.

In the Claims

Please cancel claim 56.

Please amend the following claims:

A12

2. (Amended) The method of claim 1 wherein the photosensitizer drug is texaphyrin or a derivative thereof.

3. (Amended) The method of claim 2 wherein the photosensitizer drug is lutetium texaphyrin.

A13

5. (Amended) The method of claim 1 wherein the photosensitizer drug is a benzoporphyrin or a derivative thereof.

7. (Amended) The method of claim 5 wherein the photosensitizer drug is Visudyne.

A14

8. (Amended) The method of claim 1 wherein the photosensitizer drug is a xanthene or a derivative thereof.